

Proposed Decision Memo for Carotid Artery Stenting (CAG-00085R)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) proposes the following:

The evidence is adequate to conclude that carotid artery stenting (CAS) with embolic protection is reasonable and necessary for patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis $\geq 70\%$. Coverage is limited to these procedures using FDA approved carotid artery stenting systems and embolic protection devices.

Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

- congestive heart failure (CHF) class III/IV
- left ventricular ejection fraction (LVEF) $< 30\%$
- unstable angina
- contralateral carotid occlusion
- recent myocardial infarction (MI)
- previous CEA with recurrent stenosis
- prior radiation treatment to the neck

Symptoms of carotid artery stenosis include carotid transient ischemic attack (distinct focal neurologic dysfunction persisting less than 24 hours), focal cerebral ischemia producing a nondisabling stroke (modified Rankin scale < 3 with symptoms for 24 hours or more),¹ and transient monocular blindness (amaurosis fugax). Patients who have had a disabling stroke (modified Rankin scale ≥ 3) would be excluded from coverage.

The determination that a patient is high risk and the patient's symptoms of carotid artery stenosis would be found in the patient medical records prior to performing any procedure.

The degree of carotid artery stenosis should be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis must be confirmed by angiography at the start of the procedure. If the stenosis is determined to be less than 70% by angiography, then CAS should not proceed.

In addition, CMS has determined that CAS with embolic protection is reasonable and necessary only if performed in facilities and by physicians² who have been determined to be competent in performing the evaluation, procedure and follow-up necessary to ensure optimal patient outcomes. We propose that competency will be determined through a national evaluation process by a recognized entity using approved standards. Standards will include specific physician training standards, facility support requirements and data collection to evaluate outcomes during a required reevaluation. Examples of standards and clinical competence guidelines include those recently published in the American Journal of Neuroradiology³, and those recently published in the Journal of the American College of Cardiology.⁴

Coverage of carotid artery stenting with embolic protection for patients who do not meet the indications proposed in this decision memorandum, such as patients with symptomatic carotid artery stenosis ($\geq 50\%$ and $< 70\%$) and patients with asymptomatic carotid artery stenosis ($\geq 80\%$), will be unchanged. As is the current situation, coverage for these specific groups of patients may be available in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (CAG 00259N). All other Medicare policies on PTA of the carotid artery apply.⁵

CMS is requesting public comments on this proposed decision memorandum pursuant to section 731 of the Medicare Modernization Act. CMS is particularly interested in soliciting public comments related to the following:

- Appropriate criteria, comorbid or chronic conditions for defining patients at high risk for CEA
- Criteria for appropriately defining symptomatic patients
- Professional and facility standards for performing PTA of the carotid artery with carotid stent placement
- Evaluation process for providers and facilities

After considering the public comments, CMS will issue a final decision memorandum.

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Proposed Decision Memo

To: Administrative File: CAG # 00085R.
Carotid Artery Stenting

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Subject: Proposed Coverage Decision Memorandum for Carotid Artery Stenting

Date: December 17, 2004

I. Proposed Decision

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II. Background

Each year about 700,000 people in the United States experience a new or recurrent stroke. About 500,000 of these are first attacks and 200,000 are recurrent attacks.⁶ The term stroke refers to a “group of cerebrovascular disorders in which part of the brain is transiently or permanently affected by ischemia or hemorrhage, or in which one or more blood vessels of the brain are primarily affected by a pathologic process, or both.”⁷ There are three main categories of strokes: cerebral infarction (greater than 80%), intracerebral hemorrhage, and subarachnoid hemorrhage. Of the cerebral infarctions, “20% to 30% are due to atherothrombosis or thromboembolism from the extracranial or intracranial vessels.”⁸

Risk factors for stroke include advanced age, male gender, hypertension, history of stroke or TIA (transient ischemic attack), atrial fibrillation, valvular heart disease, diabetes mellitus, carotid artery stenosis, hypercoagulable conditions, and cigarette smoking. Hypertension is “the single most important risk factor for both ischemic and hemorrhage stroke.”⁹

Awareness of stroke warning signs is important since “the inability of patients and bystanders to recognize stroke symptoms and to quickly access the emergency medical system are the largest barriers to effective acute stroke therapy.”¹⁰ Stroke warning signs include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden confusion, trouble speaking or understanding speech
- sudden trouble seeing in one or both eyes
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden severe headache with no known cause^{11,12}

Prevention of stroke remains important and includes treatment of hypertension and diabetes mellitus, smoking cessation, limiting alcohol intake, control of diet and obesity, antiplatelet drugs or anticoagulants for atrial fibrillation and selected acute myocardial infarctions, antiplatelet drugs for symptomatic carotid or vertebrobasilar atherosclerosis, and carotid endarterectomy (CEA) for specifically defined populations of patients with symptomatic carotid artery stenosis.^{13,14, 15} CEA is a surgical procedure used to prevent stroke in which the surgeon removes fatty deposits or ulcerated and stenotic plaques from the carotid arteries, the two main arteries in the neck supplying blood to the brain. Although carotid artery stenosis is an important risk factor, it was estimated that “approximately 20% and 45% of strokes in the territory of symptomatic and asymptomatic carotid arteries with 70% to 99% stenosis, respectively, are unrelated to carotid stenosis.”¹⁶ In these patients, optimal medical therapy would be most important since CEA does not reduce lacunar and cardio embolic strokes.

Carotid artery stenting (CAS) is performed with a catheter, usually inserted through the femoral artery, and threaded up to the carotid artery beyond the area of narrowing. A distal embolic protection device or filter is usually placed first to catch emboli or debris that may dislodge during the procedure. A self-expandable or balloon-expandable, metal mesh stent is then placed to widen the stenosis and the protection device is removed.

III. History of Medicare Coverage

On June 18, 2004 CMS began a national coverage determination process for carotid artery stenting (CAS) with embolic protection for patients at high risk for CEA. Previously, Medicare covered PTA (percutaneous transluminal angioplasty) of the carotid artery concurrent with stent placement in accordance with the Food and Drug Administration (FDA) approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials and in FDA required post approval studies. According to the CIM 50-32 (NCD Manual 20.7) Effective July 1, 2001, PTA of the carotid artery, when provided solely for the purpose of carotid artery dilation concurrent with carotid stent placement, is considered to be a reasonable and necessary service only when provided in the context of such a clinical trial, and therefore is considered a covered service for the purposes of these trials. Effective October 12, 2004, Medicare covers PTA of the carotid artery concurrent with the placement of an FDA-approved carotid stent for an FDA-approved indication when furnished in accordance with FDA-approved protocols governing post-approval studies. CMS determines that coverage of PTA of the carotid artery is reasonable and necessary under these circumstances.

Reconsideration

Cordis requested that CMS reconsider our position on carotid stenting and that we modify current language in the stenting PTA coverage decision to allow for coverage of carotid stenting outside of Category B IDE trials. A timeline of the background and recent developments and activities is listed below.

Discussion of Related CIMs

Medicare's NCD for PTA concurrent with carotid stenting can be found in CIM 50-32 (NCD Manual 20.7). Medicare's NCD for PTA concurrent with carotid stenting in FDA Post Approval Studies can also be found at CIM 50-32 (NCD Manual 20.7)

Benefit Category Determination

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. PTA concurrent with carotid stent placement falls under the benefit category set forth in section §1861(b)(3) (inpatient hospital services), part A benefit under §1812(a)(1) and §1861(s)(1) (physician services), a part B benefit.

IV. Timeline of Recent Activities

January 6, 2004	Cordis, a subdivision of Johnson & Johnson, submitted a letter requesting that CMS consider expanding coverage for carotid stents.
February 3, 2004	CMS received a letter of support for the potential expansion of coverage for carotid stents signed by various medical, surgical, and radiological specialty societies.
March 19, 2004	On this date a meeting was held at CMS with Medtronic to discuss the MAVeRIC II trial and their carotid stenting technologies.
April 22, 2004	CMS met with Guidant Corporation to discuss ARChR trial 12- month data and their carotid stenting technologies.
May 12, 2004	On this date a meeting was held with Cordis to go over physician training and credentialing programs, as well as facility experience.
May 27, 2004	On this date a meeting was held with Guidant to go over a proposed physician training program and facility experience requirements.
June 18, 2004	CMS opened the NCD process based on Cordis' request. Tracking sheet posted. Public comment period begins.
July 1, 2004	CMS met with the Society of Interventional Radiology to go over appropriate patient selection criteria, credentialing and training.
July 12, 2004	On this date a meeting was held with the Society for Vascular Medicine and Biology and the Society for Cardiovascular Angiography and Interventions to go over appropriate patient selection criteria, credentialing and training.
July 18, 2004	The Carotid Stenting NCA tracking sheet public comment period ended. We received 140 pages of public comments which are posted on the tracking sheet at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=128
July 21, 2004	On this date there was a meeting with the American Society of Interventional and Therapeutic Neuroradiology to go over appropriate patient selection criteria, credentialing and training.
August 10, 2004	CMS met with Abbott Laboratories to go over new clinical data for their new carotid stenting system.
August 17, 2004	A town hall meeting was held at CMS central office in Baltimore to discuss training for physicians and hospital staff for carotid stent placement. Attendees included members from medical device industry, FDA and various physician professional societies.
September 1, 2004	CMS posted its draft Decision Memo on Carotid Artery Stenting in Post Approval studies, announcing expanded coverage in these trials.
September 9, 2004	CMS met with Boston Scientific to go over their proposed physician training programs.
October 12, 2004	CMS posted final Decision Memorandum on Carotid Artery Stenting in Post Approval studies along with public comments.

V. FDA Status

FDA Section

On April 21, 2004, an FDA Advisory Panel met to review Cordis' carotid stent PMA submission and in a 6-5 decision voted to recommend approval.¹⁷ During that meeting several public commenters raised concerns over the use of carotid stenting in asymptomatic individuals, and even suggested that the labeled indication for the devices should not include asymptomatic patients, due to minimal evidence on the degree of benefit of the procedure for those patients. During the panel's deliberations, the appropriateness of using the device in the asymptomatic patient population continued to raise concerns. The panel members that voted against recommending approval consistently cited the lack of compelling evidence demonstrating benefit for carotid stenting in asymptomatic patients.

On August 31, 2004 FDA granted Guidant Corporation clearance to market their ACCULINK™ Carotid Stenting System under a PMA for the indicated treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below.

1. Patients with neurological symptoms and > 50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and > 80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

Currently, Guidant is the only manufacturer with FDA approval under a PMA (post market approval) to market their carotid stent system, although it will be possible for competitors to receive clearance for their carotid stenting devices under a PMA as well. FDA has not approved carotid artery stenting systems for use in low to moderate risk patients. Use of these devices for that indication would represent off-label use.¹⁸

Both CMS and the FDA review scientific evidence, and may review the same evidence, to make purchasing and regulatory decisions. However, CMS and its contractors make coverage determinations and the FDA conducts premarket review of products under different statutory standards and different delegated authority (67 FR 66755, November 1, 2002). Whereas the FDA must determine that a product is safe and effective as a condition of approval, CMS must determine that the product is reasonable and necessary as a condition of coverage under section 1862(a)(1)(A) of the Act. CMS adopts FDA determinations of safety and effectiveness, and CMS evaluates whether or not the product is reasonable and necessary for the Medicare population. Although an FDA-regulated product must receive FDA approval or clearance (unless exempt from the FDA premarket review process) for at least one indication to be eligible for Medicare coverage, except for Category B devices under an IDE clinical trial (see 60 FR 48417, September 19, 1995), FDA approval/clearance alone does not generally entitle that device to coverage.¹⁹ Amongst other things, CMS evaluates whether or not the intervention improves net health outcomes in the Medicare population at least as well as established treatments. Thus, FDA PMA approval alone is not sufficient for making a determination concerning Medicare coverage.

The same applies to FDA Premarket notification (510(k)) clearance. As we stated in 66 FR 58788, 58797 (November 23, 2001), "[t]he criteria the FDA uses in making determinations related to substantial equivalency under section 510(k) of the Food, Drug, and Cosmetic Act is significantly different from the scientific evidence considered in making a determination that a device is "reasonable and necessary" by Medicare. FDA does not necessarily require clinical data or outcomes studies for a determination of substantial equivalency for clearance of a device under section 510(k) of the Food, Drug, and Cosmetic Act. Medicare NCDs consider medical benefit and clinical utility of an item or service in determining whether the item or service is considered reasonable and necessary under the Medicare program. Thus, a Premarket notification cleared under section 510(k) of FDA is not sufficient for determination of Medicare coverage."

VI. General Methodological Principles

When developing NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively and 2) the intervention will improve net health outcomes for patients. A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix III. In general, features of diagnostic studies that improve quality and decrease bias include the selection of a clinically relevant inception cohort, the consistent use of a single good reference standard, the inclusion of patients with and without the disorder in question, and the blinding of readers of the index test and of reference test results.²⁰

VII. Evidence

A. Introduction

There have been several reported studies on CAS. These trials have predominantly used mortality, stroke, and myocardial infarction as primary outcomes. Since CAS is an invasive procedure, peri-procedural mortality and morbidity are important as well as long-term measures of these outcomes. In addition, the patients studied in the clinical trials can generally be classified by the presence or absence of symptoms from their carotid artery stenosis. It is important to consider these two subpopulations separately since they have differing risks of stroke and benefits of intervention. Since all trials have compared CAS to CEA, a basic review of CEA trials and evidence is required to establish the basis for comparisons.

B. Discussion of evidence reviewed

1. Questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: “Is the evidence sufficient to conclude that the application of the technology under study will improve net health outcomes for Medicare patients?”

The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared and the delivery setting. In this reconsideration, CMS sought to address the following questions:

- Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with symptomatic carotid artery stenosis and who are at high risk for surgery?

- a. What degree of stenosis should be treated?
- Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with asymptomatic carotid artery stenosis > 80% and who are at high risk for surgery?

2. External technology assessments

No external technology assessment were found or commissioned.

3. Internal technology assessments

Medline was iteratively searched from 1992 using the following keywords: carotid artery stenting. Studies on animal subjects and reports in languages other than English were excluded.

Five original randomized clinical trials, 10 other studies, presentations, and review articles were considered. Summaries of the major trials on CEA have also been included.

A. Carotid Artery Stenting

I. Randomized Trials

In terms of study design, the randomized trial or experiment offers the best design for controlling the influence of confounding variables and the strongest evidence for inference, assuming it has been conducted properly. For CAS, there were 5 published trials that compared CAS to CEA.

*Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy. Stroke 2001;32:325-d.*²¹

In 2001, Alberts reported the results of a randomized trial of 219 patients with symptomatic CAS of 60-99% by cerebral angiogram. The primary outcome was ipsilateral stroke, procedure-related death, or vascular death within 1 year. Patients were randomly assigned to CAS (n= 107) or CEA (n= 112). Patients in the stent group were treated with the WALLSTENT endoprosthesis, aspirin (325 mg bid) and ticlopidine (250 mg bid) for 4 weeks. The primary end-point rate at approximately one year was 12.1% in the stent group and 3.6% in the CEA group (p = 0.022). The study did not find that CAS was equivalent to CEA and was terminated early due to lack of efficacy in the CAS group. The author noted that “this study did not find that carotid stenting was equivalent to CEA in patients with symptomatic CAS (carotid artery stenosis).”²²

Brooks WH, McClure RR, Jones MR, et al. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: A randomized trial in a community hospital. Neurosurgery 2004;54:318-325.

In 2004, Brooks and colleagues reported the results of a randomized clinical trial designed to compare carotid angioplasty and stenting to CEA for the treatment of asymptomatic carotid artery stenosis. The primary outcome was not specified. Inclusion criteria included asymptomatic internal carotid stenosis > 80% as determined by NASCET criteria, life expectancy of 5 years and ability to sign an informed consent. Exclusion criteria included any symptom of cerebrovascular ischemia, cardiac arrhythmia, and history of bleeding diathesis or coagulopathy.

A total of 85 patients were enrolled. Of these, 44 patients were randomly assigned to CAS and 42 to CEA. All patients received 325 milligrams (mg) of aspirin and 75 mg of clopidogrel. Mean age was approximately 67 years in the CAS group and 70 years in the CEA group. Proportions of males and females were not reported. The follow-up period was 48 months.

The investigators reported that “patency of the reconstructed artery remained satisfactory regardless of the technique as determined by sequential ultrasound.”²³ No deaths occurred. No cerebral ischemia was reported. The investigators concluded that “CAS and CEA may be equally effective and safe in treating individuals with asymptomatic carotid stenosis.”²⁴

In this study, there was a small sample size. The trial was conducted at one hospital. There was no medical therapy or control group. Distal embolic protection devices were not used.

Brooks WH, McClure RR, Jones MR, et al. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. J Am Coll Cardiol 2001; 38:1589-1595.

In 2001, Brooks and colleagues reported the results of a randomized clinical trial to compare carotid angioplasty and stenting to CEA for the treatment of symptomatic carotid artery stenosis. The primary outcome was not specified. Inclusion criteria included the following: events confined to the carotid circulation within 3 months of evaluation; > 70% stenosis of the ipsilateral carotid bifurcation as determined by NASCET criteria; and anticipated life expectancy of five years. Exclusion criteria included NIH stroke scale of > 4, cardiac arrhythmia, and patients with symptoms of vertebral-basilar insufficiency or intracranial occlusive disease shown by cerebral angiography.

A total of 104 patients were enrolled. Of these, 53 patients were randomly assigned to CAS and 51 to CEA. All patients received 325 mg of aspirin and 75 mg of clopidogrel. Mean age was approximately 66 years in the CAS group and 70 years in the CEA group. Proportions of males and females were not reported. Average follow-up time was not reported.

The investigators reported that “patency of the reconstructed artery remained satisfactory regardless of the technique as determined by sequential ultrasound.”²⁵ No deaths and 1 transient ischemic attack (TIA) occurred in the CAS group. One death and no TIA occurred in the CEA group. No strokes occurred in either group. The investigators concluded that “carotid stenting is equivalent to CEA in reducing carotid stenosis without increased risk for major complications of death/stroke.”²⁶

In this study, there was a small sample size. The trial was conducted at one hospital. There was no medical therapy or control group. Distal embolic protection devices were not used.

CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Lancet 2001;357:1729-1737.

CAVATAS was a prospective, randomized clinical trial designed to test the hypothesis that endovascular treatment (balloon dilation or use of a stent) of carotid stenosis would have the same major complication rates and less minor morbidity than CEA. The primary outcome was death or any stroke. Inclusion criteria included stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment. Investigators used their own protocol to determine the need for treatment. Exclusion criteria included medical or surgical risk factors such as recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis.

A total of 505 patients were enrolled. Of these, 251 patients were randomly assigned to endovascular treatment and 253 to surgical treatment. One patient was excluded due to carotid occlusion. Mean age was 67 years. Men comprised about 70% of the study population. About 97% of the patients had cerebrovascular symptoms within 6 months before randomization. An independent neurologist evaluated patients. Stents suitable for use in the carotid arteries were developed during the course of the study and used in 55 patients.

There were 25 events (7 deaths and 18 strokes; 10% event rate) in the endovascular group compared to 25 events (4 deaths and 21 strokes; 10% event rate) in the surgical group within 30 days. The investigators concluded that “endovascular treatment had similar major risks and effectiveness at prevention of stroke during 3 years compared with carotid surgery.”²⁷

In this study, there was no medical therapy or control group. There was no uniform protocol for inclusion. Stents were used in 55 patients. All patients received antiplatelet therapy. Distal embolic protection devices were not used.

Yadav JS, Wholey MH, Kuntz KE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-1501.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was a prospective, randomized trial designed to test the hypothesis that CAS was not inferior to CEA. The primary outcome was cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. The trial was designed as a non-inferiority trial.

Inclusion criteria included symptomatic carotid artery stenosis and greater than 50% occlusion of one or more of the carotid arteries, as measured by angiography or ultrasound. Neurologic symptoms were assessed by a neurologist. Patients with no symptoms were also included if they had carotid artery stenosis greater than 80% of the luminal diameter. Increased risk was defined as having at least one of the following: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery or radiation therapy to the neck, recurrent stenosis after endarterectomy, or age > 80 years.

Exclusion criteria included ischemic stroke within previous 48 hours, presence of intraluminal thrombus, total occlusion of target vessel, vascular disease precluding use of catheter-based techniques, intracranial aneurysm >9 mm in diameter, need for more than 2 stents, history of bleeding disorder, percutaneous or surgical intervention planned within next 30 days, life expectancy < 1 year, and ostial lesion of common carotid artery or brachiocephalic artery.

A total of 747 patients were enrolled in the trial. Of these, 334 patients were randomly assigned to either carotid artery stenting with embolic protection (n= 167) or carotid endarterectomy (n= 167). Patients who received CAS were also treated with 75 mg of clopidogrel per day for 2-4 weeks. Mean age was 73 years. About 20% of patients were > 80 years. Men comprised 67% of the study population. Approximately 30% of patients in the CAS group had symptomatic stenosis. Approximately 28% of patients in the CEA group had symptomatic stenosis. Degree of stenosis was not reported.

The primary endpoint occurred in 20 patients (12.2%) in the stenting group compared to 32 patients (20.1%) in the endarterectomy group (p= 0.004 for noninferiority). The investigators reported that “among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy.”²⁸

In this trial, there was 1:1 randomization to the treatment groups. A large proportion (55%) of the patients who were enrolled in the study was not randomly assigned to treatment. There was no medical therapy or control group. Only patients who underwent CAS received clopidogrel therapy. Average follow-up time was not reported. Symptoms of carotid artery stenosis were not specifically reported. The trial was ended early due to decreased enrollment.

III. Ongoing Trials on CAS

Several trials comparing CAS to CEA are ongoing and summarized below:

CREST - Carotid Revascularization Endarterectomy versus Stent Trial²⁹

Study Design: Prospective, randomized, clinical trial on lower risk patients.

Inclusion Criteria: Patients who have experienced a TIA, amaurosis fugax (AF), or non-disabling stroke within the past 180 days, and who have an ipsilateral carotid stenosis > 50% by angiography or 70% by ultrasound will be eligible.

Exclusion Criteria: Patients who have comorbid conditions that interfere with the evaluation of endpoints, that are known to interfere with the completion of CEA or CAS, or that affect the likelihood of survival for the 4-year study period, will be excluded.

Patient Involvement: Eligible patients will be randomized to undergo either CAS or CEA. All will receive aspirin, antiplatelet therapy, treatment for hypertension, and management of other stroke risk factors. Follow-up will last four years.

Primary Outcome: Death, stroke, or myocardial infarction at 30 days postoperatively; ipsilateral stroke at 60 days postoperatively.

EVA-3S *Endarterectomy Versus Angioplasty in patients with Severe Symptomatic carotid Stenosis*³⁰

Study Design: Prospective Randomized Open Blinded End-point (PROBE) Study.

Inclusion Criteria: Patients presenting within 4 months of ischemic cerebral or retinal stroke will be eligible.

Patient Involvement: Eligible patients will be randomized to undergo either carotid endarterectomy or angioplasty with stenting. Angioplasty patients will receive either ticlopidine or clopidogrel for 1 month after the procedure. Patients in both groups will receive follow-up visits at 1 month, 6 months, and every 6 months thereafter for 2 - 4 years. Duplex scans will be performed at the time of the procedure, and every 6 months for the duration of the study. Patients in the angioplasty group will undergo blood draws at 15 days and 1 month, and a simple cervical radiogram at 2 years after the procedure.

Primary Outcome: All mortality and all recurrence of stroke within 30 days, all ipsilateral stroke within 2 - 4 years.

ICSS (CAVATAS-2) - *International Carotid Stenting Study*³¹

Study Design: Open, prospective, randomized, multicenter trial.

Inclusion Criteria: Patients older than 40 years with symptomatic severe ($\geq 70\%$), whose carotid stenoses are suitable for primary stenting and surgical endarterectomy, who are able to begin treatment as soon as possible after randomization, and who have no indication or contraindication to either treatment will be eligible.

Exclusion Criteria: Patients who have had a major stroke with minimal recovery of function in the territory of the artery in question, who are unsuitable for stenting due to tortuous anatomy proximal or distal to the stenosis, the presence of a visible thrombus, proximal carotid artery stenotic disease, pseudo-occlusion, high stenosis, or rigid neck, who are medically unfit for surgery, or who have a life expectancy < 2 years will be excluded.

Primary Outcome: Incidence of mortality and debilitating (modified Rankin score (MRS) < 3 for 30 days after onset) stroke.

Study Design: Prospective, randomized, independently-controlled, multicenter trial.

Inclusion Criteria: Patients with severe carotid stenosis ($\geq 70\%$ by Duplex sonography, $\geq 50\%$ by NASCET criteria, or $\geq 70\%$ by ECST criteria) who have experienced amaurosis fugax, TIA, prolonged reversible ischemic neurological deficit (PRIND), or other mild stroke within 180 days of randomization, amaurosis fugax, or non-disabling stroke (mod. Rankin ≤ 3) occurring within 180 days will be eligible.

Exclusion Criteria: Pregnant females, and persons with a history of intracranial bleeding within 90 days of randomization, who have a confirmed arteriovenous malformation or aneurysm, who have a serious comorbid illness limiting life expectancy < 2 years, who have an uncontrolled coagulopathy, who have any contraindication for heparin, ASA, clopidogrel, or contrast media, who have stenosis or dissection of the common and/or internal carotid arteries, who have stenosis following surgical or endovascular pretreatment, whose stenoses result from radiation therapy, fibromuscular dysplasia, or endovascular thrombosis, who have tandem stenoses (if the distal stenosis is the more severe), who have other planned surgical interventions, or who have any comorbid condition that, in the opinion of the investigator, would interfere with the study, will be excluded.

Primary Outcome: 30-day incidence of ipsilateral cerebrovascular events (cerebral infarction and/or hemorrhage with symptoms lasting for more than 24 hours); 30-day mortality.

II. Other Published or Presented Studies on CAS

The following case series, cohort or registry type studies may provide supporting evidence but, given the lack of a comparison or control group and other weaknesses inherent to the design of these types of studies, definite inferences cannot usually be made.

*ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHER) 1, 2, 3.*³³

The ARCHER studies were prospective registries designed to evaluate CAS in patients who are at high risk for CEA. Inclusion criteria included symptomatic carotid stenosis $\geq 50\%$ or asymptomatic stenosis $\geq 80\%$. Patients had to have at least one risk factor, such as uncontrolled diabetes, LVEF $< 30\%$, or previous radical neck surgery. The primary outcomes for ARCHER 1 and 2 were the composite of death, stroke and MI at 30 days plus ipsilateral stroke from 31 days to 1 year. In ARCHER 3, the primary outcome was the composite of death, stroke and MI at 30 days to confirm the outcomes of ARCHER 2 using rapid-exchange equipment.

In ARCHER 1, 158 patients were included and received CAS without distal protection. In ARCHER 2, 278 patients were included and received CAS with distal protection. In ARCHER 3, 145 patients were included.

At 30 days, the composite of death, stroke, and MI was 7.6%, 8.6%, and 8.3% for ARCHER 1, 2, and 3, respectively. Adding ipsilateral stroke from 31 days to 1 year, the composite was 8.3% and 10.2% for ARCHER 1 and 2, respectively.

*Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH).*³⁴

BEACH was a prospective registry designed to evaluate the outcomes of patients with carotid artery stenosis at high-risk for CEA. The primary endpoint was the composite of 30 day MI, death and stroke; and ipsilateral stroke and death from day 31 to 1 year. Inclusion criteria included symptomatic stenosis $\geq 50\%$ and asymptomatic stenosis $\geq 80\%$ by angiography. Exclusion criteria included recent stroke, cardiac emboli, and total occlusion of ipsilateral artery.

A total of 480 patients were studied. Mean age was 71 years. Men comprised 65% of the study population. At 30 days, there was a 5.4% rate for the composite endpoint of stroke, MI and death. The study is ongoing.

*Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent (CABERNET).*³⁵

The CABERNET study was a prospective registry designed to evaluate the outcome of patients who are at high risk for CEA that were treated with CAS. The primary outcome was the 30 day composite of mortality, stroke and MI. Inclusion criteria included symptomatic stenosis $\geq 50\%$ or asymptomatic stenosis $\geq 80\%$ by ultrasound or $\geq 60\%$ by angiogram.

A total of 443 patients were included in the registry. At 30 days, the composite endpoint of mortality, stroke and MI was 3.8%.

*CARESS Steering Committee. Carotid Revascularization using Endarterectomy or Stenting Systems (CARESS): Phase I clinical trial. J Endovasc Ther 2003;10:1021-1030.*³⁶

CARESS (Phase I) was a prospective, nonrandomized trial designed as “an equivalence cohort study to determine whether the stroke/death rate following carotid stenting with cerebral protection was comparable to CEA, the standard of care for patients with symptomatic and asymptomatic carotid stenosis.”³⁷ Another objective was to obtain an estimate of the 30-day primary endpoint (death and/or stroke from any cause). The presence or absence of stroke was determined by neurologic examinations by an independent neurologist. Patients with symptomatic stenosis $\geq 50\%$ and asymptomatic stenosis $\geq 75\%$ were included.

A total of 439 patients were enrolled. Of these, 397 were treated: 254 with CEA and 143 with carotid stenting systems (CSS). Mean age was 71 years. Men comprised about 62% of the study population. The committee reported that “there was no significant difference in the 30-day combined all-cause mortality and stroke rate by Kaplan-Meier estimate between CEA (2%) and CSS (2%).”³⁸

*Cordis Smart Self-Expandable Stent in Carotid Artery Disease (CASCADE).*³⁹

The CASCADE study was a prospective registry of 121 patients. Inclusion criteria included stenosis between the origin of the common carotid artery and extracranial segment of the internal carotid artery and either symptomatic stenosis > 70% or asymptomatic stenosis > 85% by ultrasound or angiography. The primary outcome was ipsilateral stroke or procedural related death within 30 days of stent implantation. Overall 7.4% of the study population had an ipsilateral stroke. There were no deaths at 30 days. For patients who had CAS with embolic protection, 3.2% had an ipsilateral stroke compared to 8.9% for patients without embolic protection.

Cremonesi A, Manetti R, Setacci F, Setacci C, Castriota F. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. Stroke 2003;34:1936-1943.

In 2003, the investigators reported the results of a study to evaluate in-hospital and 30-day adverse events for patients undergoing CAS with embolic protection. A total of 442 consecutive patients with symptomatic carotid artery stenosis > 75% were treated. The authors stated: "The percutaneous procedure was successful in 440 of 442 patients (99.5%). No periprocedural death occurred with any embolic protection device. All in-hospital stroke/death and 30-day ipsilateral stroke/death rate was 1.1%. The overall complication rate was 3.4%. Major adverse events included 1 major stroke (0.2%), 4 intracranial hemorrhages (0.9%), 1 carotid artery wall fissuration (0.2%), and 1 diffuse cardioembolism (0.2%)."⁴⁰

*Medtronic AVE Self-Expanding Carotid Stent System in the Treatment of Carotid Stenosis II (MAVERIC II).*⁴¹

The MAVERIC II study was a prospective registry designed to evaluate the safety and efficacy of CAS for patients at high risk for CEA. The primary outcome was a composite of death, ipsilateral stroke and MI at 1 year. The secondary outcome was a composite of death, ipsilateral stroke and MI at 30 days. A total of 339 patients were included in the registry. The primary outcome was not presented. The secondary outcome at 30 days was 5.3%.

Reimers B, Schluter M, Castriota F, et al. Routine use of cerebral protection during carotid artery stenting: results of a multicenter registry of 753 patients. Am J Med 2004;116:217-222.

In 2004, the investigators reported the results of a prospective registry that was designed to evaluate procedural and 30 day outcomes of a consecutive series of carotid stent procedures with cerebral protection. All patients had $\geq 70\%$ stenosis of the internal or common carotid artery, measured according to the NASCET criteria. There were 753 patients and 815 carotid artery lesions. Mean age was 70 years. Men comprised 74% of the patients. Of the lesions, 26% were symptomatic. Mean diameter stenosis was 83%.

Of the 815 interventions, 808 were considered successful. A stent was placed in 801 of the lesions. There were 30 major events (3.7%) within 30 days; 4 deaths (0.5%), 23 nonfatal strokes (2.7%), and 3 nonfatal myocardial infarctions (0.4%). The investigators concluded that “in this uncontrolled study, routine cerebral protection during carotid artery stenting was technically feasible and clinically safe.”⁴²

Roubin GS, New G, Iyer SS, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis. Circulation 2001;103:532-537.

The investigators reported the results of a prospective study designed to better define the incidence of immediate and late outcomes such as stroke and death in a large series of patients undergoing CAS. Inclusion criteria were symptomatic stenosis of the carotid artery $\geq 50\%$ or asymptomatic stenosis $\geq 60\%$. Exclusion criteria included major neurological deficit, severe renal insufficiency, severe diffuse atherosclerosis of the common carotid artery, and chronic total occlusions.

A total of 528 patients were included and underwent CAS. Mean age was 69 years. Men comprised 67% of the study population. At 30 days, there were 43 deaths and strokes (8.1%). After 30 days, the incidence of late stroke was 3.2% over a mean follow-up time of 17 months. The investigators reported that “experience from a single group of operators demonstrates that carotid stenting can be performed with an acceptable 30-day complication rate.”⁴³

SSLYVIA Investigators. Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYL VIA) study results. Stroke 2004;35:1388-1392.

The SSLYVIA study was a prospective, nonrandomized study designed to evaluate stenting in patients with symptomatic atherosclerotic disease of the extracranial vertebral and intracranial arteries. The primary outcomes were death or stroke within 30 days and stent success.

Patients between 19 and 80 years old with TIA or stroke due to a single atherosclerotic stenosis $\geq 50\%$ of an extracranial vertebral or intracranial artery by angiography. Exclusion criteria included intracranial hemorrhage or hemorrhagic stroke within 30 days, intracranial tumors, and cerebral arteriovenous malformations.

A total of 61 patients were enrolled including 15 patients with carotid artery lesions. Mean age was 63.6 years. Men comprised 82% of the study population. At the study endpoint, there were no deaths and 4 strokes. The stent was successfully placed in 58 of the 61 patients (95%). There were 2 strokes in the 15 patients (13%) with carotid artery lesions. The investigators reported that “strokes occurred in 6.6% of patients within 30 days and in 7.3% between 30 days and 1 year.”⁴⁴

III. Carotid Endarterectomy

European Carotid Surgery Trialists' Collaborative Group. Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-1387.

The ECST was a randomized trial designed to compare CEA (as soon as possible) to best medical therapy (avoiding surgery if possible). The primary outcome was major stroke or death. The main objective of the prespecified analysis was to estimate the range of stenosis within which CEA showed benefit. Inclusion criteria included one or more carotid territory ischemic events in the brain or eye in the previous 6 months. Exclusion criteria included distal carotid artery disease more severe than proximal disease, and embolism from the heart to the brain or eye.

A total of 3024 patients were randomly assigned to CEA surgery (n= 1811) and control (n= 1213). Mean age was 62 years. Men comprised 72% of the study population. Mean follow-up was 6.1 years. Of the patients assigned to surgery, 62 did not undergo CEA. Of the patients assigned to control therapy, 143 underwent CEA. There were 669 (37%) major strokes or deaths in the CEA group compared to 442 (36.5%) in the control group. Reductions in the numbers of major strokes or deaths occurred in patients with stenosis of $\geq 70\%$ (39% in the CEA group compared to 44% in the control group).

The investigators concluded that “carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%.”⁴⁵ They also noted that “age and sex should also be taken into account in decisions on whether to operate.”⁴⁶

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-1428.

ACAS was a randomized trial designed to test whether CEA should be a component of management for selected patients with asymptomatic stenosis of the common carotid bulb, the internal carotid sinus, or both. The main outcome was all strokes or deaths occurring within 30 days after randomization in the surgical and 42 days in the medical groups. Secondary analyses included any stroke and perioperative death and any stroke and any death.

Inclusion criteria included age between 40 and 79 years and hemodynamically significant carotid stenosis, defined as meeting one of three criteria: arteriography within the previous 60 days indicating stenosis $\geq 60\%$; Doppler examination within the preceding 60 days showing a frequency or velocity greater than the instrument-specific cut point with 95% positive predictive value; or Doppler examination showing a frequency or velocity greater than the instrument-specific cut point with 90% positive predictive value cut point confirmed by ocular pneumoplethysmographic examination performed within the previous 60 days. Exclusion criteria included cerebrovascular events in the distribution of the study carotid artery or in that of the vertebrobasilar arterial system; symptoms referable to the contralateral cerebral hemisphere within the previous 45 days; a disorder that could seriously complicate surgery; or a condition that could prevent continuing participation or was likely to produce disability or death within 5 years.

A total of 1662 patients were randomly assigned to CEA (n= 825) or medical therapy (n= 834). Mean age was 67 years. Men comprised 66% of the study population. After a median follow-up of 2.7 years, there was a significant reduction in the composite endpoint of ipsilateral stroke and any perioperative stroke or death (risk reduction= 0.53; 95% CI= 0.22-0.72). There was no significant difference for the measure of any stroke or death (risk reduction= 0.20; 95% CI= -0.02-0.37). There was no significant difference in total deaths (83 in the surgical group compared to 89 in the medical group).

The investigators reported that “patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors.”⁴⁷

Hobson RW, Weis DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221-227.

In 1993, the Veterans Affairs Cooperative Study group reported the results of a randomized trial designed to determine the effect of CEA compared to optimal medical treatment. The primary outcome was the combined incidence of TIA, transient monocular blindness, and stroke. Inclusion criteria included male gender and asymptomatic carotid stenosis \geq 50%. Exclusion criteria included prior stroke, prior endarterectomy with restenosis, and life expectancy < 5 years.

A total of 444 patients were enrolled and randomly assigned to either CEA (n= 211) or optimal medical therapy (n= 233). Mean age was 64.5 years. Mean follow-up was 47.9 months. There was a significant reduction in the incidence of TIA, transient monocular blindness, and stroke in the CEA group compared to the medical group (12.8% versus 24.5%, respectively; p-value < 0.002). There were no significant differences between groups for ipsilateral stroke alone, stroke and death within 30 days, and all strokes and deaths. The observed differences were predominately due to differences in the outcomes of TIA and transient monocular blindness.

Mayo Asymptomatic Carotid Endarterectomy Study Group (MACE)⁴⁸

MACE was a prospective, randomized trial to compare the effects of carotid endarterectomy with medical treatment of low-dose aspirin in patients with asymptomatic carotid stenosis. The primary outcome was TIA, ischemic or hemorrhagic stroke in any vascular territory, and death.

Inclusion criteria included no history of symptoms of cerebral or retinal ischemic disease and carotid stenosis but not occlusion on duplex ultrasound scans or intravenous digital subtraction angiograms. Exclusion criteria included age less than 18 years or greater than 79 years, contraindication to aspirin, prior allergic reaction to contrast dye, unstable angina or myocardial infarction within previous 6 months, potential sources of cardiac embolus, moderate to severe congestive heart failure, severe obstructive pulmonary disease, terminal illness, and dementia.

The trial was terminated early on December 10, 1990 (total n= 71) due to a significantly higher number of MIs and transient cerebral ischemic events in the surgical group compared to the medical group.

MRC (Medical Research Council) Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. Lancet 2004;363:1491-1502.

ACST was a prospective, randomized trial designed to assess the net long term effects of CEA on overall stroke risk and on fatal or disabling stroke among patients with substantial carotid artery narrowing, but with no relevant neurological symptoms in the previous 6 months. The main trial outcomes were perioperative mortality and morbidity (stroke and myocardial infarction) and the incidence of non-perioperative stroke. Inclusion criteria included unilateral or bilateral carotid artery stenosis $\geq 60\%$ on ultrasound that did not cause stroke, TIA, or other neurological symptoms in the past 6 months. Exclusion criteria included previous ipsilateral CEA, poor surgical risk, cardiac source of emboli, or any other major life-threatening condition.

A total of 3120 patients were randomly assigned to immediate CEA (n= 1560) or deferral of CEA until a definite indication was thought to have arisen (n= 1560). Mean age was 68 years. Men comprised 68% of the study population. Mean follow-up was 3.4 years.

During the first 5 years after randomization, there were 1348 CEAs performed in the immediate CEA group and 229 CEAs performed in the deferred CEA group. There were 15 deaths, 25 strokes, and 10 nonfatal MIs within 30 days of CEA in immediate group compared to 2 deaths, 9 strokes, and 0 nonfatal MIs in the deferred CEA group. At five years, there was a significant reduction in the combined outcome of any type of stroke or perioperative death in the immediate CEA group compared to the deferred CEA group (6.42% versus 11.78%; $p < 0.001$), with survival curves crossing at about 2 years.

The investigators reported that “in asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of who were on aspirin, antihypertensive, and in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard).”⁴⁹ They further stated that “outside trials, inappropriate selection of patients or poor surgery could obviate such benefits.”⁵⁰

North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-453.

NASCET (first phase) was a prospective, randomized trial designed to determine whether CEA reduces the risk of stroke among patients with a recent adverse cerebrovascular event and ipsilateral carotid stenosis. The primary outcome was any ipsilateral stroke at 2 years. Inclusion criteria included age < 80 years, hemispheric TIA or monocular blindness or nondisabling stroke within previous 120 days, and stenosis of 30 to 99% in the ipsilateral internal carotid artery. Exclusion criteria included more severe intracranial lesion; organ failure of kidney, liver, or lung; cerebral infarction; cardiac valvular or rhythm disorder likely to be associated with cardioembolic symptoms; or prior ipsilateral CEA.

A total of 662 patients were enrolled. Of these, 328 patients were randomly assigned to CEA and 331 to the medical therapy group, while 3 patients were excluded. Median age was about 66 years. Men comprised about 69% of the study population. Mean follow-up was 18 months. At 2 years, there was a significant reduction in ipsilateral stroke in the CEA group compared to the medical group (risk reduction=17%, $p < 0.001$). There was a significant reduction in the composite of any stroke or death in the CEA group compared to the medical group (risk reduction=16.5%, $p < 0.001$). There were 15 deaths in the CEA group compared to 21 deaths in the medical group.

The investigators reported that “carotid endarterectomy is highly beneficial to patients with recent hemispheric and retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99 percent) of the internal carotid artery.”⁵¹

Barnet HJM, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998;339:1415-1425.

The first phase of the NASCET focused on patients with symptomatic stenosis $\geq 70\%$ and was completed in 1991. The second phase of NASCET continued and focused on patients with symptomatic stenosis $< 70\%$. The primary outcome was any fatal or nonfatal ipsilateral stroke. Inclusion criteria included symptoms of focal cerebral ischemia ipsilateral to a stenosis of less than 70% in the internal carotid artery within 180 days, as shown on selective angiography, and persisting less than 24 hours or producing a nondisabling stroke. Exclusion criteria were similar to the first phase of NASCET but patients over 80 years of age were no longer specifically excluded.

A total of 2267 patients were randomly assigned to CEA (n= 1108) or medical therapy (n= 1118). Median age was 66 years. Men comprised about 70% of the study population. Mean follow-up was 5 years. A total of 858 patients had symptomatic stenosis of 50-69%, and 1368 patients had symptomatic stenosis $< 50\%$. For the primary outcome of any fatal or nonfatal ipsilateral stroke, there was a modest difference for patients with symptomatic stenosis of 50-69% in the CEA group compared to the medical group (15.7% versus 22.2%, respectively; p-value= 0.045). There was no significant difference for patients with symptomatic stenosis $< 50\%$ in the CEA group compared to the medical group (14.9% versus 18.7%, respectively; p-value= 0.16).

The investigators stated: "Endarterectomy in patients with symptomatic moderate carotid stenosis of 50 to 69 percent yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if carotid endarterectomy is to be performed. Patients with stenosis of less than 50 percent did not benefit from surgery. Patients with severe stenosis (≥ 70 percent) had a durable benefit from endarterectomy at eight years of follow-up."⁵²

Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. N Engl J Med 2000;342:1693-1700.

In 2000, Inzitari and colleagues reported the results of additional analyses of the NASCET data. They reported: “The risk of stroke at five years after study entry in a total of 1820 patients increased with the severity of stenosis. Among 1604 patients with stenosis of less than 60 percent of the luminal diameter, the risk of a first stroke was 8.0 percent (1.6 percent annually), as compared with 16.2 percent (3.2 percent annually) among 216 patients with 60 to 99 percent stenosis. In the group with 60 to 99 percent stenosis, the five-year risk of stroke in the territory of a large artery was 9.9 percent, that of lacunar stroke was 6.0 percent, and that of cardioembolic stroke 2.1 percent. Some patients had more than one stroke of more than one cause. In the territory of an asymptomatic occluded artery (as was identified in 86 patients), the annualized risk of stroke was 1.9 percent.”⁵³

4. Medicare Coverage Advisory Committee (MCAC)

CMS did not convene an MCAC for this issue.

5. Evidence-based Reviews and Professional Society Guidelines

Brott TG, Roberts J, HJobson RW, Hughes S. Carotid revascularization in 2004. Endovascular Today 2004;3:33-40.

In 2004, Brott and colleagues reported the results of an evidence-based review on CEA and CAS studies. They reported: “The SAPHIRE and ARCHeR 30-day results are not ideal, particularly for asymptomatic patients. These results raise the question as to whether medical therapy alone may be superior to carotid revascularization in high-risk patients, whether CEA or CAS. For high-risk patients, higher periprocedural morbidity, concurrent illness, and higher stroke risk outside the territory of the treated carotid could counterbalance or even exceed the benefits of revascularization. In asymptomatic patients at high risk, data suggesting urgent need for carotid artery revascularization are lacking. For example, the stroke and death rates of the highrisk asymptomatic patients in SAPHIRE and ARCHeR at 1 month are well above the recommended American Heart Association Guidelines of a 30-day stroke and death rate of $\leq 3\%$. In addition, the 1-year stroke rates for asymptomatic SAPHIRE patients of 7.7%, and the composite 1-year endpoint rate for asymptomatic ARCHeR 1 and 2 patients of 8.3% and 10.2%, respectively, approach the 5-year ipsilateral stroke rates of the patients treated medically in ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST (Asymptomatic Carotid Surgery Trial).”⁵⁴

Brott TG, Brown RD, Meyer FB, Miller DA, Cloft HJ, Sullivan TM. Carotid revascularization for prevention of stroke: carotid endarterectomy and carotid artery stenting. Mayo Clin Proc 2004;79:1197-1208.

In 2004, Brott and colleagues reported the results of an evidence-based review on CEA and CAS studies. They reported: “The SAPHIRE and ARCHeR 30-day results are not ideal and raise the question of whether medical therapy alone may be superior to carotid revascularization (CEA or CAS) in high-risk patients. Except for NASCET (North American Symptomatic Carotid Endarterectomy Trial), the NNT (number needed to treat) for symptomatic and asymptomatic patients in all the large RCTs (Tables 1 and 2) is modest in moderate-risk patients. For high-risk patients, higher periprocedural morbidity, concurrent illness, and higher stroke risk outside the territory of the treated carotid artery could counterbalance or even exceed the benefits of revascularization.”⁵⁵

Connors JJ, Sacks D, Furlan AJ, et al. Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention. Am J Neuroradiol 2004;25:1732-1741.

In 2004, the American Academy of Neurology, the American Association of Neurological Surgeons, the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, the Congress of Neurological Surgeons, and the Society of Interventional Radiology released a consensus statement that addressed carotid artery stenting. The consensus statement stated the following:⁵⁶

1. All collaborating neuroscience societies are of the unanimous opinion that the safety of the patient is paramount.
2. Defined formal training and experience in both the cognitive and technical aspects of the neurosciences are essential for the performance and interpretation of diagnostic and therapeutic cervical and cerebrovascular procedures.
3. All collaborating neuroscience societies endorse the principles of the several published standards from our various societies for training and quality concerning cervicocerebral angiography and intervention.
4. All collaborating neuroscience societies recommend appropriately supervised cervicocerebral angiography training and resultant credentialing with an accumulated total of 100 diagnostic cervicocerebral angiograms before post-graduate training in cervicocerebral interventional procedures, including carotid stenting.
5. All collaborating neuroscience societies endorse the principles of training and quality assurance espoused in the multisociety Quality Improvement Guidelines for the Performance of Carotid Angioplasty and Stent Placement, which include a defined training pathway for any qualified practitioner for carotid stent training.

6. All collaborating neuroscience societies specifically endorse the principles of the ACGME and the training programs in Endovascular Surgical Neuroradiology, Vascular Neurology and Neuroradiology.

Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev 2004:CD000515.

In 2004, Coward and colleagues reported the results of an evidence-based review “to assess the benefits and risks of endovascular treatments compared with carotid endarterectomy (in patients suitable for surgery) or medical therapy (in patients not suitable for surgery).”⁵⁷

Four completed trials were reviewed. The authors reported: “Data from randomized trials comparing endovascular treatment for carotid artery stenosis with carotid endarterectomy suggest that the two treatments have similar early risks of death or stroke and similar long term benefits. However, the substantial heterogeneity renders the overall estimates of effect somewhat unreliable. Furthermore, two trials were stopped early because of safety concerns, so perhaps leading to an over-estimate of the risks of endovascular treatment. On the other hand, endovascular treatment appears to avoid completely the risk of cranial neuropathy. There is also uncertainty about the potential for restenosis to develop and cause recurrent stroke after endovascular treatment. The current evidence does not support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis. There is a strong case to continue recruitment in the current randomized trials comparing carotid stenting with endarterectomy.”⁵⁸

Creager MA, Goldstone J, Hirshfeld JW, et al. ACC/ACP/SCAI/SVMB/SVS clinical competence statement on vascular medicine and catheter-based peripheral vascular interventions: A report of the American College of Cardiology/American Heart Association/ American College of Physicians Task Force on Clinical Competence (ACC/ACP/SCAI/SVMB/SVS Writing Committee to develop a clinical competence statement on peripheral vascular disease). JACC 2004;44:941-957.

In 2004, the American College of Cardiology (ACC), the American College of Physicians (ACP), the Society for Cardiovascular Angiography and Interventions (SCAI), the Society for Vascular Medicine and Biology (SVMB), and the Society for Vascular Surgery (SVS) released a clinical competence statement that included a section on carotid artery stenting. They reported: "Obtaining competence in the performance of procedures and interventions in the extracranial cerebral vessels (i.e., carotid and vertebral arteries) is considered a unique category on the following bases: first, although there is crossover in the technical skills from other vascular territories, unique challenges are associated with cannulating the carotid and vertebral arteries and performing interventions in these circulatory beds; and second, there are obvious special issues related to the distribution and target organ of these vessels, which allow for very narrow safety margins. For those performing carotid or vertebral procedures, suggested requirements for achievement of competence include mastery of the cognitive and clinical skills pertaining specifically to this vascular bed and these procedures. This includes, as with other sites, a complete understanding of the anatomical and pathological characteristics unique to this vascular bed and the ability to interpret relevant angiographic images. To achieve competence, a minimum of 30 diagnostic cerebrovascular angiograms, 15 as supervised primary operator, and a minimum of 25 supervised interventions, at least one-half as primary operator, should be performed, with appropriate documentation, follow-up, and outcomes assessment. The recommended number of procedures reflects the consensus of the expert opinion of the committee. It is acknowledged that catheter-based intervention of the extracranial cerebral arteries is an area of competence that is in evolution. Accordingly, these recommendations may be modified in future documents as experience and clinical evidence regarding its safety and efficacy is acquired. Also, as with procedures in other regional vascular venues, it is anticipated that for some physicians to achieve competence, supervising faculty will recommend additional cases beyond the minimum number."⁵⁹

O'Rourke F, Dean N, Akhtar N, Shuaib A. Current and future concepts in stroke prevention. CMAJ 2004;170:1123-1133.

In 2004, O'Rourke and colleagues reported the results of an evidence-based review on interventions used for stroke prevention. For CEA, the authors wrote: "Carotid endarterectomy of a symptomatic severe stenosis of an internal carotid artery remains one of the most effective methods of preventing recurrent stroke, reducing the risk by up to two thirds. The number-needed to-treat (NNT) to prevent 1 stroke at 2 years is 8 for high grade stenosis ($\geq 70\%$) and 20 for moderate stenosis (50%–69%). Endarterectomy for asymptomatic stenosis of the internal carotid artery remains controversial. Although one study demonstrated a 53% relative risk reduction in ipsilateral stroke and death over 5 years, the number of events was small, with a higher NNT and men appeared to benefit considerably more than women. Long-term benefits may also be outweighed by the early risks of excess perioperative stroke or death (relative risk [RR] 6.52, 95% CI 2.66–15.96) and are influenced by the complication rates of individual surgeons. Guidelines suggest that surgery should be considered only for asymptomatic carotid disease if the complication rate is less than 3% and the stenosis is greater than 60%. The age and health of the patient, plaque stability and presence of coexisting cerebral artery disease should also be considered."⁶⁰

Halm EA, Chassin MR, Tuhim S, et al. Revisiting the appropriateness of carotid endarterectomy. Stroke 2003;34:1464-1472.

In 2003, Halm and colleagues reported the results of an investigation to determine the appropriateness and use of CEA since the publication of the major trials. They used the RAND appropriateness method to assess CEA performed by 67 surgeons in 1997 to 1998 in 6 hospitals. The authors reported: “In conclusion, since the large public investment in RCTs of carotid endarterectomy, rates of overuse appear to have fallen dramatically, although they are still significant. There has been a major shift toward operating on asymptomatic patients who have much less to gain from carotid endarterectomy compared with those who are symptomatic. Although overall complication rates among these 6 hospitals were comparable to the benchmark performance of the highly selected RCT sites, the adverse event rates among asymptomatic patients with high comorbid illness burden exceeded recommended thresholds.”⁶¹

American Heart Association

In 1995, the AHA released guidelines for CEA that stated:

“Indications for carotid endarterectomy in symptomatic good-risk patients with a surgeon whose surgical morbidity and mortality rate is less than 6% are as follows: (1) *Proven*: one or more TIAs in the past 6 months and carotid stenosis $\geq 70\%$ or mild stroke within 6 months and a carotid stenosis $\geq 70\%$; (2) *acceptable but not proven*: TIAs within the past 6 months and a stenosis 50% to 69%, progressive stroke and a stenosis $\geq 70\%$, mild or moderate stroke in the past 6 months and a stenosis 50% to 69%, or carotid endarterectomy ipsilateral to TIAs and a stenosis $\geq 70\%$ combined with required coronary artery bypass grafting; (3) *uncertain*: TIAs with a stenosis $< 50\%$, mild stroke and stenosis $< 50\%$, TIAs with a stenosis $< 70\%$ combined with coronary artery bypass grafting, or symptomatic, acute carotid thrombosis; (4) *proven inappropriate*: moderate stroke with stenosis $< 50\%$, not on aspirin; single TIA, $< 50\%$ stenosis, not on aspirin; high-risk patient with multiple TIAs, not on aspirin, stenosis $< 50\%$; high-risk patient, mild or moderate stroke, stenosis $< 50\%$, not on aspirin; global ischemic symptoms with stenosis $< 50\%$; acute dissection, asymptomatic on heparin. Indications for carotid endarterectomy in asymptomatic good-risk patients performed by a surgeon whose surgical morbidity and mortality rate is less than 3% are as follows: (1) *Proven*: none. As this statement went to press, the National Institute of Neurological Disorders and Stroke issued a clinical advisory stating that the Institute has halted the Asymptomatic Carotid Atherosclerosis Study (ACAS) because of a clear benefit in favor of surgery for patients with carotid stenosis $\geq 60\%$ as measured by diameter reduction. When the ACAS report is published, this indication will be re-categorized as proven. (2) *acceptable but not proven*: stenosis $> 75\%$ by linear diameter; (3) *uncertain*: stenosis $> 75\%$ in a high-risk patient/surgeon (surgical morbidity and mortality rate $> 3\%$), combined carotid/coronary operations, or ulcerative lesions without hemodynamically significant stenosis; (4) *proven inappropriate*: operations with a combined stroke morbidity and mortality $> 5\%$.”⁶²

6. Professional Society Position Statements

CMS received position papers from various medical societies expressing support for expanded coverage for carotid artery stenting for the high-risk patient population. All professional societies were in favor of expanded coverage; however, there was considerable variation with respect to the specific patient population that would likely benefit from this treatment, how to identify that patient population, the degree of expertise/credentialing needed to perform stenting, and the need for a mandatory data collection as part of a national evaluation process.

The Society of Interventional Radiology (SIR): Supports expanded coverage for carotid stenting for patients at high risk for CEA, however SIR cautions that expanded coverage should be carefully limited to the right patient subgroup and recommends that the application of this technology to asymptomatic patients be restricted to patients with additional medical and anatomic conditions. With respect to physician competency and training, SIR in conjunction with ASITN (American Society of Interventional and Therapeutic Neuroradiology) and ASNR (American Society of Neuroradiology) drafted, “Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent placement.” According to SIR acceptable physician qualifications included but are not limited to: “Performance (under the supervision of a qualified physician and with at least 50% performed as the primary operator) of at least 200 diagnostic cervicocerebral angiograms with documented acceptable indications and outcomes.”⁶³ As part of patient management SIR strongly suggests that CMS require an independent neurological evaluation pre-and post- stenting procedure. SIR advocates that facilities intending to provide carotid stenting have in place the same infrastructure required for CEA, appropriate imaging equipment and providers with substantial knowledge of cerebrovascular anatomy, knowledge of the clinical and imaging evaluation of patients with cerebrovascular disorders, including knowledge of the clinical manifestations and the natural history of cerebrovascular ischemic disease. Finally, SIR is supportive of mandatory outcomes reporting on a national level, to monitor patient outcomes.

The Society of Vascular Surgeons (SVS): Advocates the expansion of coverage, and recommends guarding against an over-proliferation of the procedure by creating an objective, independent, mandatory data collection mechanism. SVS, ACC (American College of Cardiology), SIR SCAI (The Society for Cardiovascular Angiography and Interventions) and SVMB (Society for Vascular Medicine and Biology) advocate that the carotid stenting registry should be audited and nationally monitored. With regard to physician training, SVS believes that physicians must have knowledge of all treatment options for extracranial cerebrovascular disease, and must demonstrate clinical competency as described in a SVS, ACC, ACP, SCAI, SVMB joint clinical competence statement on Vascular Medicine and Catheter-based Peripheral Vascular Interventions. With respect to physician expertise, the parties above believe, “To achieve clinical competence in carotid stenting, [SVS, ACC, ACP, SCAI, and SVMB] recommends performance of a minimum of 30 diagnostic cerebrovascular angiograms, 15 as a supervised primary operator, and a minimum of 25 supervised carotid interventions, at least half as primary operator.”⁶⁴SVS supports independent neurological assessment by a neurologist or other care provider with NIH stroke scale training; however it does not recommend the immediate availability of an intra cranial neurointerventionalist for neuro-rescue.

The Society for Vascular Medicine and Biology (SVMB) & The Society for Cardiovascular Angiography and Interventions (SCAI) & Society for Vascular Surgery (SVS) & The American College of Cardiology (ACC): The above mentioned groups are in agreement with expanding coverage for carotid artery stenting and have expressed general consensus on the delineation of skills and expertise that would be required to perform carotid stenting. However the level of skills that these groups suggest differs considerably from those posited by the SIR, ASITN and ASNR in the “Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent placement.” SVS, ACC, SCAI and SVMB favor less stringent guidelines with respect to provider familiarity and experience with specifically cerebrovascular interventions. Their guidelines for performing carotid stenting are set forth in the “ACC/ACP/SCAI/SVMB/SVS Clinical Competence Statement on Vascular Medicine and Catheter-Based Peripheral Vascular Interventions.” Finally, all groups strongly support of the creation of an evaluation process to help ensure good patient outcomes.

American Academy of Neurology (AAN): believes that stroke prevention is the sole indication for carotid stenting and that neurologic symptoms due to carotid disease are the primary indications for intervention. According to the AAN, neurologic symptoms due to carotid disease are difficult to discern from other neurologic ailments and therefore ANN strongly recommends that a neurologist or other physician with experience in the management of patients with cerebrovascular disease be a component in the evaluation of patient prior to the procedure. The AAN has endorsed the physician credentialing paper of the Neuroscience Coalition (comprised of The American Academy of Neurology (AAN), The American Association of Neurological Surgeons (AANS), The American Society of Interventional and Therapeutic Neuroradiology (ASITN), The American Society of Neuroradiology (ASNR), The Congress of Neurological Surgeons (CNS), the AANS/CNS Cerebrovascular Section, and the Society of Interventional Radiology (SIR)).

The American Society of Interventional and Therapeutic Neuroradiology (ASITN): is also in favor of expanded coverage for carotid artery stenting for high-risk patients. ASITN has also voiced concerns about the inappropriate use of this procedure on asymptomatic patients and maintains that medical therapy should be the standard of care for most patients with asymptomatic carotid stenosis. ASITN posits that medical therapy is the best treatment for the majority of patients with asymptomatic carotid artery stenosis and that neither CEA nor CAS should be offered to the majority of patients with asymptomatic carotid artery disease, especially in the absence of CAS trials “report[ing] morbidity and mortality rates approaching the 3% figure deemed to be necessary to achieved benefit from CEA in asymptomatic patients.”⁶⁵ Citing data from the ACAS, ACST and Cardiovascular Health study, ASITN believes that patients with asymptomatic carotid stenosis are rare (<.5% of the Medicare population)⁶⁶ and have are known to have very low rates of stroke. According to the ASITN position, “Both ACAS and ASCT have definitively proved that there is NO increasing risk with increasing degrees of stenosis in asymptomatic patients.”⁶⁷ With respect to facility requirements to perform CAS, ASITN favors the JCAHO guidelines for Primary Stroke Centers based on the Brain Attack Coalition recommendations as a model for these requirements and recognizes the need for uniform data collection on patients’ outcomes for this procedure.

7. Public Comments

After initiating the NCD process, the tracking sheet was posted marking the 30 day public comment period. During that time we received numerous comments supporting our intention to expand coverage for carotid artery stenting to high risk patients. While the comments were favorable, many commenters stressed the importance of ensuring that physicians were properly trained to perform carotid stenting. Additionally, a few commenters suggested that facilities intending to offer the procedure be high volume cardiac or vascular centers. Individual physicians, as well as those representing societies, suggested the levels of credentialing and experience physicians should have to perform carotid stenting. Comments ranged in specificity from naming the type of imaging equipment facilities should have in place to listing the number of procedures physicians should have performed prior to doing carotid stenting. There was some disparity amongst the different physician societies with respect to appropriate and adequate experience and prior interventional procedures required to successfully perform the procedure. Other comments included data on carotid stent trials by the manufacturers. Many cited inclusion criteria for these trials as factors that define the high risk patient population and also provided published articles intended to demonstrate the benefits of carotid stenting. For more details or to view the public comments please our website at: <http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=128>

VIII. CMS Analysis

National Coverage Determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a)(1)(A).

For this review of CAS, there were 5 randomized trials (CAVATAS, SAPPHIRE, 2 by Brooks et al., and 1 by Albert) and 5 published case-series, cohort or registry studies (CARESS, Cremonesi et al., Reimers et al., Roubin et al., SSYLVA). The results of 5 other studies (ARCHER series, BEACH, CABERNET, CASCADE, MAVERIC II) have been presented at national meetings.

Of the trials, the two reported by Brooks had relatively small sample sizes and were conducted in one community hospital. The trial reported by Alberts was terminated early due to a significantly higher rate of ipsilateral stroke, procedure-related death, or vascular death at the 1 year endpoint for patients undergoing CAS compared to CEA. CAVATAS was initially designed to study percutaneous transluminal (balloon) angioplasty to CEA. During the course of the trial, carotid stents became available and were then allowed as a treatment option. However, only 55 patients received a stent and the study was not specifically designed to fully evaluate CAS. The negative trial by Alberts, the 2 trials by Brooks and CAVATAS provided only limited evidence on CAS. SAPPHIRE studied more patients (n= 334) but several issues have been raised about the trial and its results that may hamper generalizability outside the restrictive setting of a randomized trial. First, the patients that were randomized were highly selected. Of the 747 patients enrolled, only 334 were randomly assigned to the treatment groups. It is very unlikely this level of selectivity, where both a surgeon and an interventionalist must agree on treatment, will be available in actual practice outside a trial. The influence of this selection process is suggested by the results of the SAPPHIRE CAS registry, which showed a higher rate of major adverse events at 360 days for asymptomatic patients compared to asymptomatic patients in the randomized CAS treatment arm (15.7% versus 10.3%, respectively).⁶⁸ Also, physicians participating in trials usually have much more experience in study procedures than physicians in actual practice settings. These factors may significantly affect the observed health outcomes of CAS outside the realms of clinical trials.

Second, patients assigned CAS were also treated with clopidogrel (75 mg per day), which has been shown in randomized controlled trials to significantly reduce the risk of cardiovascular death, MI and stroke.^{69,70} The actual length of treatment with clopidogrel was not reported in the SAPPHIRE publication, although it was likely at least 2 to 4 weeks for each patient as stated in the protocol. Since patients assigned to CEA were not treated similarly, the use of clopidogrel is a potential confounder and should be considered a co-treatment. The actual duration of treatment with clopidogrel is an important variable that should be disclosed. Since there was no medical therapy control group, the independent effects of CAS with embolic protection or clopidogrel alone cannot be determined from the SAPPHIRE trial.

In addition, Cambria noted on the SAPPHIRE trial that “the small sample size and the study end points preclude major conclusions about the relative roles of endarterectomy and carotid-artery stenting in the treatment of carotid artery stenosis. Physicians, industry sponsors, and regulatory agencies should collectively insist on large-scale, multicenter trials in order to clarify the appropriate role of carotid artery stenting in patients in different clinical and anatomical subgroups. Such trials have been initiated in North America and Europe.”⁷¹

Since all the above trials compared CAS to CEA, the fundamental assumption is that CEA is an appropriate treatment for patients in these trials. However, with advances in medical therapy and stroke prevention, the appropriateness of CEA for certain populations has been revisited. In addition, none of the CAS trials or studies included a medical therapy or control group. This situation presents a challenge in determining when to perform a procedure and when to continue best medical therapy. Optimal medical therapy has certainly changed since the trials on CEA have been completed. Estimates of stroke risk with medical therapy may have in turn changed. The influence of newer medications needs to be considered when determining the risks and benefits, and may, in many instances, reduce the appropriateness of any procedure. These issues will be discussed further in the following sections.

Since patients with symptomatic carotid artery stenosis and patients with asymptomatic carotid stenosis have different risk profiles, it would be important to consider the evidence for these groups separately for coverage.

1. Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with symptomatic carotid artery stenosis and who are at high risk for surgery?
 - a. What degree of stenosis should be treated?

Patients with symptoms from carotid artery stenosis, such as TIAs, have “a substantial short-term risk of stroke, hospitalization for cardiovascular events and death.”⁷² As noted above, all CAS trials have used CEA as the comparison group. Thus a basic understanding of CEA is important, as is a determination of when CEA is recommended. For patients with symptomatic stenosis, CEA has been shown in trials such as NASCET (first phase and second phase) and ECST to significantly reduce the risk of stroke in symptomatic patients with stenosis $\geq 70\%$. In 1991, the NASCET (first phase) investigators reported that “risk of stroke and benefit from the procedure are greatest for symptomatic patients with at least 70% stenosis of the internal carotid artery.”⁷³ They further noted that “patients with 50 to 69% stenosis experience lesser benefit, and some other groups may even be harmed by carotid endarterectomy, including women and patients with transient monocular blindness only.”⁷⁴

In 1998, the NASCET (second phase) investigators reported on a larger sample ($n=2267$) of symptomatic patients with moderate stenosis $<70\%$ and found a modest reduction in ipsilateral stroke but no difference in deaths or total strokes. They stated: “Endarterectomy in patients with symptomatic moderate carotid stenosis of 50 to 69 percent yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if carotid endarterectomy is to be performed.”⁷⁵ No benefits have been shown from CEA for patients with stenosis $< 50\%$ since the etiology of strokes in these patients is likely due to pathology in areas other than the carotid arteries.

In 1998, the ECST investigators reported the results of a randomized controlled trial on 3024 patients and noted that “on average, the immediate risk of surgery was worth trading off against the long-term risk of stroke without surgery when the stenosis was greater than 80% diameter.”⁷⁶ The investigators further noted that, “For the combined outcome of surgical events, ipsilateral major ischaemic strokes, and other major strokes, there was no overall effect below about 70-80% stenosis.”⁷⁷

Since CEA has been shown to improve health outcomes for specific patient populations, CAS may be inferred to have similar benefits if found to be noninferior or equivalent to CEA. For symptomatic patients with carotid artery stenosis $\geq 70\%$, there is evidence and agreement about the use of CEA. For CAS, SAPHIRE studied 334 patients (but only 96 high risk patients with symptomatic stenosis), and showed no significant differences between CAS and CEA for death, stroke, and MI at 360 days.⁷⁸ The degree of stenosis was not reported in the SAPHIRE trial. A trial conducted in a community hospital by Brooks and colleagues on symptomatic patients (n= 104) with stenosis $> 70\%$ showed that CAS and CEA had similar rates of death and cerebral ischemia.⁷⁹ A trial by Alberts (n=219) showed a significantly higher primary endpoint rate in patients who received CAS compared to CEA; however, the report was an abstract.⁸⁰ A complete report of the trial has not been published therefore full consideration of this trial is not possible at this time.

Several registry or cohort studies and evidence-based reviews provide supporting evidence. In 2004, O'Rourke and colleagues reported "carotid endarterectomy remains the definitive treatment in patients with symptomatic stenosis of the internal carotid artery of 70% or higher."⁸¹ In 2000, Gubitz and Sandercock reported "The benefit from surgery was related to the degree of stenosis. For people with severe stenosis (greater than 70% by angiography), surgery almost completely abolished the risk of ipsilateral stroke over several years."⁸²

Based on trial results and supporting evidence from other studies, CAS does not appear to be inferior to CEA for severe symptomatic stenosis. Thus, there is sufficient evidence to infer that CAS with embolic protection can improve health outcomes for patients with symptomatic stenosis $\geq 70\%$ who are at high risk for CEA, if performed with the same expertise and rate of adverse events as demonstrated in the published clinical trials. Since all patients who received CAS with embolic protection in the major trials received clopidogrel, it should be considered a co-treatment and administered to all patients appropriately, according to FDA recommendations.⁸³

For symptomatic patients with carotid artery stenosis $< 70\%$, NASCET (second phase) showed a benefit in ipsilateral stroke for stenosis of 50-69% but no overall benefit for any stroke and death from any cause. As noted by the trial investigators (NASCET, ECST) and by authors of evidence-based reviews, there remain concerns about the risk and benefits of CEA for patients with symptomatic carotid stenosis of 50-69%. In 2004, Barnett note that "special caution must be exercised for patients with only moderate (50%-69%) stenosis who are women or who have had ocular symptoms only."⁸⁴ In 2000, Gubitz and Sandercock reported: "People with moderate stenosis (50-70% by angiography) also benefited, although to a lesser extent, and it is generally thought that the risk of stroke is not great enough to make endarterectomy worthwhile in this group. Importantly, not all patients with operable lesions benefit from surgery; further research is ongoing to determine who might benefit most"⁸⁵ In 1998, the NASCET investigators reported: "Many patients with symptomatic stenosis of less than 70 percent will not be considered appropriate candidates for endarterectomy when the risks and benefits are carefully weighted. Our final results do not justify a large increase in the rate of endarterectomy. We recommend restraint."⁸⁶

The NIH sponsored, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is ongoing and should provide additional evidence on CEA and CAS, especially for patients with symptomatic stenosis of 50-69%, and the risk associated with any procedure.⁸⁷ CREST was designed as a prospective, randomized trial of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) as prevention for stroke in patients with symptomatic stenosis $\geq 50\%$, and has a targeted sample size of 2500 patients, more than all prior trials combined. Several other trials on CEA and CAS (ICSS, EVA-3S, SPACE) are also ongoing.

Based on the current evidence for patients with symptomatic stenosis of 50-69%, the fundamental question of whether CEA should be performed for these patients has not been answered. If CEA cannot be generally recommended, then CAS, in turn, cannot be generally recommended. Thus, there is insufficient evidence for patients with symptomatic carotid artery stenosis $< 70\%$. This is also consistent with the recommendations of a Cochrane evidence-based review by Coward and colleagues who reported: "The data available were limited. The overall estimates of effect were both imprecise and difficult to interpret because of substantial heterogeneity. The data were therefore insufficient to support a change from routine clinical practice in the types of patients for which carotid endarterectomy is the current standard treatment. The data support the continuing inclusion of patients within randomized clinical trials between endovascular and surgical treatment for carotid artery stenosis."⁸⁸

While we await the completion of ongoing clinical trials such as CREST, ICSS, EVA-3S and SPACE, coverage for CAS with embolic protection for patients with symptomatic carotid artery stenosis of 50-69% may be available under the IDE clinical trials policy or FDA required, post market approval studies. CAS for patients with symptomatic carotid artery stenosis $< 50\%$ is not recommended.

1. Is the evidence sufficient to conclude that carotid artery stenting improves health outcomes for patients with asymptomatic carotid artery stenosis $> 80\%$ and who are at high risk for surgery?

Patients with asymptomatic carotid artery stenosis have a different risk profile than patients with symptoms. Asymptomatic patients with hemodynamically significant carotid artery stenosis have an annual stroke event rate of 2-5% (about 2% stroke occurrence per year among controls in ACST).^{89,90} In contrast, about 10.5% of patients with symptoms, such as a TIA, will have a stroke in the short term.⁹¹ While CEA has been well accepted for patients with symptomatic carotid artery stenosis $\geq 70\%$, there remains controversy for asymptomatic patients, due, in part, to the lower event rates and the development of medications, such as antiplatelet and lipid lowering drugs, for stroke prevention.

The evidence on CEA for patients with asymptomatic carotid artery stenosis was obtained mainly from the Veterans Affairs study, MACE, ACAS and ACST. The Veterans Affairs Cooperative Study did not demonstrate any significant differences in strokes and deaths between the CEA group and the optimal medical therapy group. MACE was terminated early due to a significantly higher number of MIs and TIAs in the CEA group compared to the medical group.

The ACAS and ACST showed benefits but the investigators of both these trials expressed restraint in their conclusions and targeted specific individuals. The ACAS committee reported that “patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors.”⁹² The ACST investigators reported that “in asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of who were on aspirin, antihypertensive, and in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard).”⁹³ They further stated that “outside trials, inappropriate selection of patients or poor surgery could obviate such benefits.”⁹⁴

Even to a greater degree than for patients with symptomatic stenosis 50-69%, the controversy over CEA in asymptomatic patients has been noted in evidence-based reviews, guidelines and recommendations. In 2000, Gubitz and Sandercock reported that “a systematic review of all of the available randomized data shows that the efficacy of surgery for carotid stenosis without symptoms remains unproved and that further randomized trial evidence is needed; trials are ongoing.”⁹⁵ In 2003, Halm and colleagues conducted a meta-analysis of CEA clinical trials and reported that “although overall complications rates were low, rates among asymptomatic patients with high comorbidity exceeded recommended thresholds.”⁹⁶ In 2004, Brott and colleagues stated that “best medical treatment alone in high-risk asymptomatic patients may be superior to revascularization.”⁹⁷

In 2004, O’Rourke and colleagues reported that “we do not currently recommend surgery for asymptomatic disease, preferring to treat proven vascular risk factors aggressively with immediate follow-up in the event of any stroke symptoms.”⁹⁸ In 2004, Barnett noted in a commentary on the ACST: “Before concluding that the route has been cleared to the operating room for most patients with asymptomatic carotid stenosis, several factors require careful consideration. First, patients must recognize that with good medical care they face only a 2% annual stroke rate, which falls below 1% after successful carotid endarterectomy. But the benefits will exceed the risks only if the operative hazards remain low, otherwise they could be obliterated. Contemporary reports suggest that the rates of operative complications often exceed by 1 or 2% the low rates achieved by trial surgeons (3%).^{6,7} Thus, if such surgery is to be offered, audited results of surgeon’s operative records should be readily available to referring physicians and patients. Institutions and departments should require totally independent audits of surgical morbidity rates and ensure their ready availability.”⁹⁹

In 2004, Barnett further reported in an evidence-based commentary on carotid endarterectomy (CE in this excerpt): “Two large trials involving asymptomatic patients have presented evidence that there is modest benefit favoring CE in subjects with stenosis but no symptoms, provided that highly skilled surgeons are involved and that complication rates are below 3%. Even with this low operative complication rate, the number needed to treat to prevent 1 stroke in 2 years is 83. In the 2 large trials involving a total of nearly 4500 patients, the annual stroke and death rate after CE was 1%, versus 2% among those without CE. What we do not know is whether this 2% could be reduced by a strictly supervised regimen of best modern medical care, including control of blood pressure, diabetes mellitus, lipids and cigarette smoking, along with appropriate ASA therapy. A trial of CE versus tightly controlled (as opposed to standard) medical care is one of the last remaining major trials still required to complete our knowledge of the role of CE in stroke prevention in asymptomatic patients.”¹⁰⁰

For CAS with embolic protection, SAPHIRE studied 237 high risk patients with asymptomatic carotid artery stenosis > 80%. There was no significant difference in the 30 day major adverse event rates and the 360 day major adverse event rates between CAS with embolic protection and CEA (6.0% versus 9.6% at 30 days; and 19.2% and 10.3% at 360 days, respectively).¹⁰¹ As noted above, there were several factors with the SAPHIRE trial that may hamper generalizability, such as the relatively small sample size, patient selection, physician experience, and lack of a medical therapy group. These factors may lead to a much higher rate of major adverse events in actual practices than seen in SAPHIRE, creating a situation where the risks outweigh the benefits of CAS, especially for asymptomatic patients who have, in general, a lower natural stroke rate than patients with severe symptomatic stenosis.

Additional evidence on CAS for patients with asymptomatic stenosis should also be forthcoming. The CARESS Phase II trial should provide important data and evidence on risks and benefits of CAS in this population. The CARESS Phase II trial was designed “to assess the equivalence of the procedures in nonrandomly but concurrently assigned reverse ratios of 2,000 CSS patients to 1,000 CEA patients.”¹⁰² The primary endpoint will be the combined rate of all-cause mortality and non-fatal stroke at 48 months. Patients with symptomatic stenosis \geq 50% and asymptomatic stenosis \geq 75% will be included.

Overall, there remains considerable controversy on the risks, benefits and appropriateness of CEA for patients with asymptomatic carotid artery stenosis. In general as noted by Barnett, patients with asymptomatic carotid stenosis who received good medical care are at low risk for stroke. Complication rates in actual practice from CEA often may exceed the reduction in risk from surgery. Although SAPHIRE indicated that CAS was not inferior to CEA, the appropriateness of any procedure, CAS or CEA, remains unclear. In addition, relatively few patients with asymptomatic stenosis have been studied in CAS randomized trials. No trial has evaluated long term outcomes. No trial has compared CAS to medical therapy. These types of trials are much needed and should be completed.

Based on currently available evidence, we believe that there is insufficient evidence to conclude that CAS with embolic protection improves health outcomes for patients with severe asymptomatic carotid artery stenosis > 80% and who are at high risk for CEA. While we await the completion of ongoing clinical trials such as the CARESS Phase II trial, coverage for CAS with embolic protection for patients with asymptomatic carotid artery stenosis > 80% may be available under the IDE clinical trials policy or FDA required, post market approval studies.

IX. Additional Considerations

1. Stroke Prevention

Optimal medical therapy remains a crucial aspect of stroke prevention for all patients, especially patients with asymptomatic carotid artery stenosis. Brott and colleagues noted that “better antihypertensive treatments, including the availability of ACE inhibitors and ACE receptor antagonists, improved antiplatelet regimens, potential for tighter glucose control in diabetes, and well-tolerated lipid-lowering regimens provide a potent armamentarium for the medical approach to treatment of asymptomatic carotid artery disease in high-risk patients.”¹⁰³

Since all patients who received CAS with embolic protection in the major trials received clopidogrel, it should be considered a co-treatment and administered to all patients appropriately, according to FDA recommendations.¹⁰⁴

Behavior modifications with smoking cessation and adequate physical activity are also important, as well as increasing awareness of stroke warning signs. In the SAPHIRE trial, clopidogrel was given to all patients undergoing CAS and thus should be considered a co-treatment.

2. Age and Life Expectancy

Very few patients over the age of 75 years have been studied in the CEA or CAS trials. Even fewer patients over the age of 80 years have been considered. In NASCET (first phase) and ACAS, patients with age > 80 years were not included. In ACST, there was no significant difference between immediate CEA and deferral for patients > 75 years of age. In SAPHIRE, the primary outcome (cumulative incidence of death, stroke, or MI within 30 days after procedure or death or ipsilateral stroke between 31 days and 1 year) was considerably higher (2x) for patients \geq 75 years compared to patients < 75 years of age (22% versus 11%, respectively).¹⁰⁵ With the reported lack of benefit and the higher adverse event rate, use of CEA and CAS should not be generally recommended for patients \geq 75 years, especially patients with limited life expectancy.

3. Determination of the Degree of Carotid Artery Stenosis.

In the CEA and CAS trials, both ultrasonography and angiography have been used to determine the degree of carotid artery stenosis. In NASCET and ECST, angiography was used to determine the degree of stenosis. In ACAS, Doppler ultrasonography and angiography were used. If a patient did not have an angiogram on screening, it was performed prior to CEA. In ACST, ultrasonography and angiography were used although angiography was not a requirement like in ACAS. In CAVATAS, most investigators chose digital subtraction angiography as the confirmatory test. In the 2 community trials by Brooks, angiography was used to determine the degree of stenosis. In the SAPHIRE trial, color duplex ultrasonography was used with no requirement for angiography; however, the analyses of all measurements were performed by a core laboratory.

Although ultrasonography has been used, carotid artery angiography (digital subtraction) should be considered “the gold standard in the diagnosis of carotid artery stenosis.”¹⁰⁶ Since carotid artery angiography has associated risks, the angiography can be performed at the beginning of the scheduled CAS with embolic protection. However, if the degree of stenosis is determined to be less than 70% by the angiography, then the CAS procedure should not proceed.

3. Independent Neurological Assessment

Pre-procedure and post-procedure neurological examinations were required and usually performed by independent neurologists in the major published clinical trials, including NASCET, ECST, ACAS, ACST, and SAPPHERE. Pre-procedure and post-procedure neurological examinations by a neurologist were also recommended by the Society of Interventional Radiology and the American Academy of Neurology.

4. Provider Training & Credentials

The primary responsibility to assure that physicians who perform CAS with embolic protection have appropriate qualifications, high quality training and are competent to perform these procedures resides with the hospitals where the procedures will be performed. However, CMS believes the training and experience required for CAS should be as rigorous as the training and experience required for coronary interventions, such as coronary artery stenting. Physician qualifications should be fully documented and maintained in the hospital record keeping system. Provider volume is an important factor for many procedures such as CEA and most likely CAS as well.

CMS recommends at minimum the following professional credentials (more specific physician guidelines can be found in the *American Journal of Neuroradiology*¹⁰⁷, and the *Journal of the American College of Cardiology*)¹⁰⁸:

- Experience and training in the diagnosis, management and treatment of carotid artery disease and knowledge and understanding of the pathophysiology of carotid artery disease and cerebrovascular disease, including stroke.
- Previous experience and recent training in carotid artery angiography.
- Previous experience and recent training in endovascular procedures and stent placement.
- Successful completion of a CAS training program including simulator training and proctored cases of CAS with embolic protection by expert physicians.

5. Facility Standards:

Hospitals that provide CAS with embolic protection will have appropriate staff and facilities for performing this service. Access to a state of the art intervention suite that includes adequate monitoring equipment and availability of emergency medical personnel should be available. In addition, the facility will be certified as being appropriately staffed and equipped to perform CAS with embolic protection by a credentialing entity approved by a nationally sanctioned body. Designation as an acute stroke center by JCAHO should also be considered. For CEA, Barnett reported that “low-volume hospitals with high complication rates would be wise to refer appropriate patients for endarterectomy to hospitals with more experienced surgeons.”¹⁰⁹ This should likewise apply to CAS with embolic protection.

CMS recommends at minimum the following facility standards:

- Experienced team trained to manage carotid artery disease and cerebrovascular disease.
- Experience with carotid stenting procedures.
- State of the art intervention suite that includes adequate monitoring equipment and availability of emergency medical personnel.
- Diagnostic and support services for full evaluation and follow up including: cardiology; anesthesiology; immunology; infectious disease; pulmonology; nephrology; neurology, social services; patient education; nutrition; radiology and nursing.

CMS believes that the professional staff, infrastructure and support system available at facilities intending to offer carotid stenting procedures are critical in ensuring good patient outcomes. These are the elements that will likely factor into the appropriate assessment of the patient’s suitability for surgery or stenting and the successful placement of the stent and required follow up care.

Facilities and providers that routinely and repeatedly perform this procedure and follow patients for long periods of aftercare have a greater chance of successful outcomes. The volume necessary to achieve this goal is not presently known. Therefore, until center selection criteria are developed, CMS will solicit input as to the appropriate mechanism for developing and implementing center selection criteria in the future. These criteria will be necessary prior to expanding beyond the initially approved sites.

6. Facility/Provider evaluation

Due to the potentially significant morbidity and mortality of this procedure and the learning curve necessary for optimal performance. CMS will require that all facilities performing this procedure for Medicare beneficiaries undergo a national evaluation process to demonstrate competency. This national evaluation must be based on clearly defined standards established by nationally recognized groups and must be ongoing and recurring. Standards will address:

- Provider training and experience
- Facility support
- Ongoing outcomes collection

X. Proposed Conclusions

Stroke causes significant morbidity and mortality for the Medicare population. Procedures such as CEA and CAS have been used to improve health outcomes in specific subpopulations. However, these procedures carry considerable risks that may outweigh the benefits in many patients. A thorough consideration of the risks and benefits is needed on an individual basis to help make an informed decision on the choices of therapy. Stroke prevention with appropriate use of medications such as antihypertensive, antiplatelet, and lipid-lowering drugs, must be optimized and recommended. Other considerations such as smoking cessation and life style modifications are also important.

CMS proposes the following:

The evidence is adequate to conclude that CAS with embolic protection is reasonable and necessary for patients who are at high risk for CEA and who also have symptomatic carotid artery stenosis $\geq 70\%$. Coverage is limited to these procedures using FDA approved carotid artery stenting systems and embolic protection devices.

Patients at high risk for CEA are defined as having significant comorbidities, and/or anatomic risk factors (i.e. recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

- CHF class III/IV
- LVEF < 30%
- unstable angina
- contralateral carotid occlusion
- recent MI
- previous CEA with recurrent stenosis
- prior radiation therapy to the neck

Symptoms of carotid artery stenosis include: carotid transient ischemic attack (distinct focal neurologic dysfunction persisting less than 24 hours), focal cerebral ischemia producing a nondisabling stroke (modified Rankin scale < 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax). Patients who have had a disabling stroke (modified Rankin scale \geq 3) would be excluded from coverage.

The determination of high risk patients and symptoms of carotid artery stenosis would be documented in the patient medical records prior to performing any procedure.

The degree of carotid artery stenosis must be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis should be confirmed by angiography at the start of the procedure. If the stenosis is determined to be less than 70% by angiography, then CAS should not proceed.

In addition, CMS has determined that CAS with embolic protection is reasonable and necessary only if performed in facilities and by physicians¹¹⁰ who have been determined to be competent in performing the evaluation, procedure and follow-up necessary to ensure optimal patient outcomes. We propose that competency will be determined through a national evaluation process by a recognized entity using approved standards. Standards will include specific physician training standards, facility support requirements and an ongoing data collection system to evaluate outcomes during a required reevaluation. Examples of standards and clinical competence guidelines include those recently published in the *American Journal of Neuroradiology*¹¹¹, and those recently published in the *Journal of the American College of Cardiology*.¹¹²

Coverage of carotid artery stenting with embolic protection for patients who do not meet the indications proposed in this decision memorandum, such as patients with symptomatic carotid artery stenosis ($\geq 50\%$ and $< 70\%$) and patients with asymptomatic carotid artery stenosis ($\geq 80\%$), will be unchanged. As is the current situation, coverage for these specific groups of patients may be available in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the National Coverage Determination on CAS post approval studies (CAG 00259N). All other Medicare policies on PTA of the carotid artery apply.¹¹³

CMS is requesting public comments on this proposed decision memorandum pursuant to Section 731 of the Medicare Modernization Act. CMS is particularly interested in soliciting public comments related to the appropriate criteria, comorbid or chronic conditions for defining patients at high risk for CEA as well as comments on the criteria for appropriately defining symptomatic patients. In addition, we are most interested in the appropriate evaluation process to ensure competency of providers and facilities. After considering the public comments, we will issue a final decision memorandum.

[Appendix I \[PDF, 92KB\]](#)

Appendix II

General Methodological Principles of Study Design (Section VI of the Decision Memorandum)

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

[Footnotes](#) [PDF, 91KB]

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